POST-TRAINING ADMINISTRATION OF D-CYCLOSERINE, BUT NOT SODIUM BUTYRATE, RESCUES MEMORY CONSOLIDATION FOLLOWING BACTERIAL ENDOTOXIN EXPOSURE

by

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TABLE OF CONTENTS

INTRODUCTION

Following trauma or infection, activation of the innate immune system triggers the systemic release of cytokines, the cell-signaling molecules of the immune system. Microglia, the principal immune cell of the brain, detect peripheral cytokine levels and release cytokines centrally. Thus, peripheral immune system activation leads to neuroinflammation, resulting in profound biological, cognitive, and behavior effects. A growing body of research has examined the cognitive deficits associated with neuroinflammation. Recently, chronic neuroinflammation has been implicated in neurodegenerative diseases such as Alzheimer's disease (Kahn et al., 2012). However, low levels of cytokine expression are required for certain learning and memory processes (Gibertini M., 1998). Behaviorally, neuroinflammation causes sickness behavior, characterized by mood alterations, anhedonia, diminished social exploration, and diminished locomotor activity (Avitsur & Yirmiya, 1999; Castanon et al., 2001; Engeland et al., 2001; de Paiva et al., 2010). This adaptive set of responses helps the organism survive and recover. Interestingly, seemingly maladaptive cognitive deficits result from an otherwise highly adaptive immune response.

Lipopolysaccharide (LPS) is an endotoxin produced from the cell wall of Gram-negative bacteria that acts through toll-like receptor 4 (Borowski, Kokkinidis, Merali, & Anisman, 1998). Systemic administration of LPS triggers the release of pro-inflammatory cytokines within the central nervous system, leading to a variety of neurobiological and behavioral outcomes (Pugh et al., 1998; Sparkman et al., 2005a; Thomson & Sutherland, 2005; Tarr et al., 2011; Kranjac et al., 2011). LPS primarily impairs hippocampus-dependent learning and memory, including contextual fear conditioning (Pugh et al., 1998, 1999; Barrientos et al., 2002; Thomson and Sutherland, 2005; Bilbo et al., 2006;

Kranjac et al., 2011, Kahn et al., 2012), spatial learning (Shaw et al., 2001; Sparkman et al., 2005b; Terrando et al., 2010; Kahn et al., 2012), avoidance learning (Sparkman et al., 2005a; Kohman et al., 2007a,b; Tarr et al., 2011), conditioned taste aversion (Cross-Mellor et al., 2009; Chan et al., 2009), and novel object recognition (Zaltsman et al., 2012). Interestingly, LPS has been shown to have no affect on auditory fear conditioning (Pugh et al., 1998; Kahn et al., 2012), a task that is primarily dependent on the amygdala (Bailey et al., 1999; Lamprecht et al., 2009).

In our prior research, mice challenged with systemic LPS showed impaired memory consolidation and reconsolidation in a contextual fear conditioning paradigm (Kranjac et al., 2011). Our paradigm is designed to resist any confounding effects from typical sickness behavior (Kranjac et al., 2011). The mechanisms underlying LPS-induced cognitive deficits are not well understood. However, diminished levels of brain-derived neurotrophic factor (BDNF) following LPS administration may contribute to these deficits. In our previous experiment, following the LPS challenge, we found reduced brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex at 4 h but not 48 h (Kranjac et al., 2011). Since BDNF synthesis is a critical component of memory consolidation (Nader, Schafe, & Le Doux, 2000; Lee, Everitt, & Thomas, 2004), this reduction during the consolidation time frame strongly implicates it as a possible biological mechanism in the impairments we found (Kranjac et al., 2011). We also found elevated IL-1β in the hippocampus and cortex at 4 h that were not fully resolved by 48 h (Kranjac et al., 2011). This result supported prior research that strongly implicated IL-1β as a key mediator of LPS-induced behavioral effects (Barrientos et al., 2002, Kranjac et al., 2011), potentially via diminished release of BDNF. In addition to effects on BDNF,

LPS and IL-1β may also alter or impair glutamatergic receptor function in the hippocampus. LPS has been shown to reduce long-term potentiation (LTP) in the hippocampus (Zaltsman et al., 2012) and down-regulate NMDA receptor density (Biegon et al., 2002). LTP is a prominent biological analogue of learning and memory, and LTP in the hippocampus requires activation of NMDA receptors (Malenka & Nicoll, 1999).

D-cycloserine (DCS) is a partial NMDA receptor agonist at the glycine receptor site (Hood, Compton, & Monahan, 1989). As a partial agonist, DCS displays about 40–70% of the efficacy of glycine, the endogenous ligand at this site (Dravid et al., 2007). In healthy rodents, DCS administration enhances learning and memory in many paradigms. DCS improves performance on tasks that involve the hippocampus, such as object recognition (Bado et al., 2011), object location memory (Assini, Duzzioni, & Takahashi, 2009), spatial memory (Temple & Hamm, 1996; Pitkänen et al., 1995), and hippocampus-dependent latent extinction (Gabriele & Packard, 2007). DCS also improves performance on amygdala-dependent tasks, including the elevated-plus maze retest paradigm (Rodgers, Harvest, Hassall, & Kaddour, 2011), fear conditioning (Lee, Milton, & Everitt, 2006; Yamada, Zushida, Wada, & Sekiguchi, 2009), and conditioned freezing (Ledgerwood, Richardson, & Cranney, 2003). Most interpretations of these effects suggest that DCS modulates neuroplasticity in the hippocampus and basolateral amygdala (Myers & Davis, 2006; Waddell et al., 2010; Ledgerwood et al., 2003).

DCS has also restored spatial memory in several rat models of traumatic brain injury, including lateral fluid percussion (Temple & Hamm, 1996), medial septal lesion (Riekkinen, Ikonen, & Riekkinen, 1998), and hippocampal lesion (Schuster & Schmidt, 1992). In a mouse model of closed head injury, DCS improved motor functions and

object recognition and restored BDNF in the hippocampus (Yaka et al., 2007). Following an intracisternal LPS challenge, mice administered intraperitoneal (i.p.) DCS showed restored novel object recognition, restored LTP in the hippocampus, reduced regional neuroinflammation, and up-regulated NMDA receptor density (Zaltsman et al., 2012).

Memory formation, and LPS-induced deficits thereof, involve changes in gene expression. In the nucleus of a cell, DNA is wrapped tightly around histones. The presence or absence of acetyl groups contributes to the tightness of DNA wrapped around histones, and gene transcription is partially regulated by histone acetylation and de-acetylation. Histone deacetylases (HDAC) are enzymes that cause the histone to wrap more tightly, thereby decreasing gene transcription (Reolon et al., 2011). HDAC inhibitors (HDACi), a new class of anti-inflammatory drugs, have recently been used to treat several inflammatory diseases in clinical trials. Although the precise molecular mechanism is unclear, HDACi administration results in diminished pro-inflammatory and elevated anti-inflammatory cytokine production (Blanchard & Chipoy, 2005). Sodium butyrate (NaB), one particular HDACi, exerts a strongly anti-inflammatory effect following LPS exposure in rat primary hippocampal slice cultures (Huuskonen et al., 2004). Interestingly, a recent line of research has examined the effects of HDACi on learning and memory. In rodents, NaB enhances memory formation and extinction when administered immediately before training (Lattal, Barett, & Wood, 2007; Levenson et al., 2004). In rats, post-training NaB administration restored age-related deficits in memory consolidation and retention on a novel-object recognition task (Reolon et al., 2011). Although the precise mechanisms are unclear, increased selective gene transcription by HDACi may underlie these effects on memory.

In our set of experiments, we hypothesized that post-training LPS administration would impair memory consolidation. We expected these cognitive deficits to result from elevated IL-1β and diminished BDNF within the hippocampus. In our first experiment, we hypothesized that concomitant DCS administration would rescue these LPS-induced deficits. We expected that DCS would restore hippocampal BDNF that was diminished by LPS. In our second experiment, we hypothesized that concomitant NaB administration would rescue LPS-induced deficits in memory consolidation. We expected that NaB would counteract the LPS-induced elevation of IL-1β, and that NaB would increase BDNF expression.

METHOD

Experimental Subjects

Subjects were experimentally-naïve, male C57BL/6J mice bred at the Texas Christian University (TCU) vivarium from breeding stock purchased from The Jackson Laboratory (Bar Habor, ME). Mice in experiment one were 4–6 months old, while mice in experiment two were 23 months old. After weaning at one month of age, animals were housed in groups of 3–4 in standard polycarbonate mouse cages (30 cm x 20 cm x 16 cm) at ambient temperature (22˚C) with *ad libitum* access to food and water. The light-dark cycle was set to 0700 h on and 1900 h off, and behavioral tests were conducted between 0900 h and 1100 h. Animal care was in compliance with the *Guide for the Care and Use of Laboratory Animals*, and the experiment protocols were approved by the Institutional Animal Care and Use Committee at TCU. We used 36 mice in experiment 1 and 31 mice in experiment 2.

Treatment Conditions

Intraperitoneal (i.p.) injections of LPS (*Escherichia coli*, serotype 0111:B4; Sigma, St. Louis, MO) were administered at the dose of 250 μg/kg, i.p. injections of DCS (Sigma, St. Louis, MO) were administered at the dose of 15 mg/kg, and i.p. injections of NaB (Sigma, St. Louis, MO) were administered at the dose of 1.2 g/kg in sterile, pyrogen-free 0.9% saline (Baxter, Deerfield, IL). Prior research in our lab showed that this dosage of LPS reliably induces sickness behavior and memory deficits (e.g. Kranjac et al., 2011), and is consistent with other studies involving behavioral measures of LPS-treated rodents (Pugh et al., 1998; Sparkman et al., 2005a,b; Kohman et al., 2007a,b). This dosage of DCS is commonly used in studies examining the effects of DCS on memory consolidation in both hippocampus-dependent (Gabriele & Packard, 2007) and amygdala-dependent tasks (Mickley et al., 2012; Rodgers et al., 2011). The dosage of NaB is consistent with a prevous study that examined the effects of post-training NaB administration on hippocampal-dependent memory in aged mice (Reolon et al., 2011).

Behavioral Testing Apparatus

We used fully automated units (FreezeFrame, Coulbourn Instruments, Whitehall, PA, USA) to assess conditioned contextual fear learning. Each unit contained an electrified grid floor, through which a mildly aversive shock (0.7 mA) was delivered. To enhance context salience, we incorporated a visual cue (i.e., dotted pattern walls) and an olfactory cue (i.e., peppermint odor) into each unit. Cameras in each unit, connected to the FreezeFrame software (Coulbourn Instruments, Whitehall, PA, USA), enabled continuous recording and analysis of freezing behavior. When animal movement dropped

below level 10 (the company's default setting) on a motion detection sensitivity scale (scale range: 0–1000), the behavior counted as freezing.

Experiment 1: LPS and DCS

In our first experiment, mice were randomly divided into 4 groups in a 2 (condition: LPS or saline) x 2 (treatment: DCS or saline) design. On training day, each mouse was placed into a conditioning chamber. After a 90 s acclimation period, mice received three 0.7 mA shocks, each 90 s apart. After another 90 s, each mouse was removed from the conditioning chamber and immediately administered an i.p. injection of LPS or sterile, volume-equivalent saline, followed by a second i.p. injection of DCS or sterile saline. Mice were then returned to their home-cages. As DCS has a half-life of 180 minutes (Löscher, Wlaz, Rundfeldt, Baran, & Hönack, 2009), we waited 48 hours before testing the mice, in order to avoid effects of DCS on memory recall. On test day, 48 hours after training day, mice were again placed in the conditioning chambers, but no shock was administered. We analyzed freezing behavior during the first 90 s the mice were in the chamber. Typically, if the mouse froze in the chamber on test day, then it successfully paired the context with the shock.

Experiment 2: LPS and NaB

In our second experiment, mice were randomly divided into 4 groups in a 2 (condition: LPS or saline) x 2 (treatment: NaB or saline) design. The contextual fear conditioning procedure was identical to experiment 1. Immediately post-training, mice were administered an i.p. injection of LPS or sterile, volume-equivalent saline, followed by a second i.p. injection of NaB or sterile saline. Because NaB has a half-life of 5 min

(Daniel et al., 1989), it would have no direct effect on memory recall on the test day, 48 hours later.

Statistical Analyses

All data were analyzed with standard 2 (condition) x 2 (treatment) between-subjects analyses of variance (ANOVA) at $\alpha = .05$. In experiment 1, the between-subjects variables were condition (LPS or saline) and treatment (DCS or saline). In experiment 2, the between-subjects variables were condition (LPS or saline) and treatment (NaB or saline). Significant main effects were further explored with simple main effects analyses, using a Bonferroni adjustment. Data in figures are expressed as the mean ± standard error of the mean. All data were analyzed using SPSS Statistics 20.0.0 software (IBM, Armonk, NY).

RESULTS

General Appearance and Weight Loss

In our first experiment, weights on day 1 did not differ by condition or treatment (Fs(1, 32) ≤ 3.98, ps ≥ .05). Forty-eight hours after LPS and/or DCS administration, LPS-treated mice lost a significant but small amount of weight ($F(1, 32) = 19.61$, $p \leq .001$, $\eta^2 = .37$). However, DCS administration did not affect weight loss, and DCS and LPS treatments did not interact (Fs(1, 32) ≤ .94, ps ≥ .34). Regardless of treatment (DCS or saline), mice that were administered LPS lost more weight ($M = .68$ g, $SEM = .093$) than mice administered saline ($M = .10$ g, $SEM = .093$).

In our second experiment, weights on day 1 did not differ by condition or treatment (Fs(1, 27) ≤ 1.37, ps ≥ .25). Forty-eight hours after LPS and/or NaB administration, LPS-treated mice lost a significant but small amount of weight ($F(1, 27)$

= 152.43, $p \leq .001$, $\eta^2 = .84$). However, NaB administration did not affect weight loss, and NaB and LPS treatments did not interact (Fs(1, 27) ≤ 1.42, ps ≥ .24). Regardless of treatment (NaB or saline), mice that were administered LPS lost more weight (M = 1.84 g, SEM = .10) than mice that were administered saline (M = .13 g, SEM = .10).

Experiment 1: LPS and DCS

During training, percent of time freezing during the initial 90 s (i.e. before the first shock) did not differ by condition or treatment (Fs(1, 32) ≤ 1.97, ps ≥ .17). Percent of time freezing during the initial 90 s of testing varied by condition ($F(1, 32) = 4.26$, $p \leq .05$, $\eta^2 = .09$), by treatment ($F(1, 32) = 7.98$, $p \leq .01$, $\eta^2 = .16$), and by an interaction of condition and treatment ($F(1, 32) = 5.29$, $p = .03$, $\eta^2 = .11$). Overall, the LPS condition groups froze less than the saline condition groups, and the DCS treatment groups froze more than the saline treatment groups (see Figure 1 and Table 1).

Tests for simple main effects showed differences between treatment groups (DCS or saline) within condition (LPS or saline). For mice injected with LPS, DCS treated mice froze more than saline treated mice (see Figure 1 and Table 1; $F(1, 32) = 13.14$, $p \leq .001$). For mice injected with saline (i.e. instead of LPS), DCS treated mice and saline treated mice did not differ on percent time freezing (see Figure 1 and Table 1; $F(1, 32) = .14$, $p \geq .71$).

In this paradigm, more time freezing indicates a stronger pairing of the aversive stimulus with the context. Taken together, these results suggest that LPS impaired contextual fear memory consolidation, and DCS restored this endotoxin-induced impairment in contextual fear memory consolidation. Moreover, DCS alone did not enhance contextual fear memory consolidation.

Experiment 2: LPS and NaB

During training, percent of time freezing during the initial 90 s (i.e. before the first shock) did not differ by condition or treatment (Fs(1, 27) ≤ .55, ps ≥ .47). Percent of time freezing during the initial 90 s of testing varied by condition ($F(1, 27) = 13.27$, $p \leq .001$, $\eta^2 = .32$), but not by treatment or an interaction of condition by treatment (Fs(1, 27) ≤ .83, ps ≥ .37). Regardless of treatment (NaB or saline), mice administered LPS froze less than mice administered saline (see Table 2).

Tests for simple main effects found no differences between treatment groups (NaB or saline) within condition (LPS or saline). Regardless of LPS or saline administration, NaB treated groups froze the same amount as saline-treated groups (see Figure 2 and Table 2; Fs(1, 27) ≤ .92, ps ≥ .35). However, tests for simple main effects found differences between condition groups (LPS or saline) within treatment (NaB or saline). For NaB treated groups, LPS administered mice froze less than saline-administered mice (see Figure 2 and Table 2; $F(1, 27) = 10.74$, $p \leq .003$). For saline treated groups (i.e. instead of NaB), LPS administered mice froze marginally, but not significantly, less than saline-administered mice (see Figure 2 and Table 2; $F(1, 27) = 3.61$, $p \geq .07$).

These results suggest that LPS impaired contextual fear memory consolidation. NaB did not restore this LPS-induced deficit to baseline, and NaB alone did not enhance contextual fear memory consolidation.

DISCUSSION

We hypothesized that post-training LPS administration would impair memory consolidation. This hypothesis was supported in both experiments, which is consistent

with our prior research (Kranjac et al., 2011). Also, we hypothesized that concomitant DCS administration would restore memory consolidation following a LPS challenge. This hypothesis was supported in our first experiment, and, to our best knowledge, this is a novel finding. Furthermore, we hypothesized that concomitant NaB administration would restore memory consolidation following a LPS challenge. This hypothesis was not supported by our second experiment. Finally, we found that DCS or NaB administration alone, without a LPS challenge, did not enhance memory consolidation.

Because typical sickness behavior involves diminished locomotor activity, increased sickness would result in increased freezing during the contextual fear conditioning test. LPS administration caused increase sickness, evidenced by greater weight loss, but these groups displayed higher locomotor activity (i.e., less freezing) during testing. Therefore, the effect of LPS can be attributed to memory impairment, not confounding effects of sickness behavior.

By administering LPS, DCS, and NaB immediately post-training, our effects can be attributed to changes in memory consolidation. Because DCS and NaB have short half-lives, their effects would not affect memory retrieval during testing.

Limitations

Mice in experiment one were 4–6 months old, but mice in experiment 2 were 23 months old. As older mice are more vulnerable to LPS-induced deficits (Kohman et al., 2007a), some of our results may be attributed to age. Also, we administered LPS, DCS, and NaB at one specific time point. Therefore, we cannot generalize to learning and memory processes other than memory consolidation

Current and Future Directions

After experiment 1, our lab conducted follow-up biological assays at congruent time-points to explore the underlying mechanisms of LPS and DCS co-administration. Using quantitative reverse transcription polymerase chain reaction, this experiment examined IL-1β, NMDA receptor subunits NR1 and NR2C, and BDNF mRNA levels in the dorsal hippocampus. As hypothesized, LPS administration increased IL-1β mRNA levels, while DCS had no effect on the expression of this pro-inflammatory cytokine. Similarly, as hypothesized, BDNF mRNA levels were decreased following LPS administration. However, DCS had no effect on BDNF, regardless of LPS administration. Moreover, LPS and/or DCS had no effect on the expression levels of NMDA receptor subunits NR1 and NR2C. In summary, while post-training DCS rescued LPS-induced deficits in memory consolidation, the underlying mechanisms are currently unclear (Kranjac et al., 2013). Future biological studies can examine the effects of LPS and DCS co-administration at different time-points and on various intracellular targets. Additional behavioral studies can administer LPS and DCS at different time-points in the contextual fear conditioning paradigm and examine the resulting effects on various learning and memory processes.

After experiment 2, our lab conducted several more experiments to examine the effects of LPS and NaB on hippocampus-dependent learning and memory. We tried different variations of contextual fear conditioning, with more or less aversive stimuli administered on day one. We tried different time-points of LPS and NaB administration, including repeated administration for multiple days prior to training. We also tried trace fear conditioning, a separate hippocampus-dependent memory paradigm. In several of

these experiments, we compared young and old mice to examine age-related effects of LPS and NaB administration. The results of these experiments were inconclusive. In the future, we want to examine the effects of other HDACi, such as trichostatin A, on LPS-induced deficits. If observed, a conclusive behavioral effect of NaB and LPS co-administration would warrant further biological assays to assess the underlying mechanisms.

Neuroinflammation is a complex biological process with important clinical implications. A growing body of research has examined the process by which neuroinflammation results in cognitive deficits and possible points of intervention. To this extent, the current findings contribute to the understanding of neuroinflammation-associated cognitive deficits in humans, and ways such deficits may be abrogated.

APPENDIX

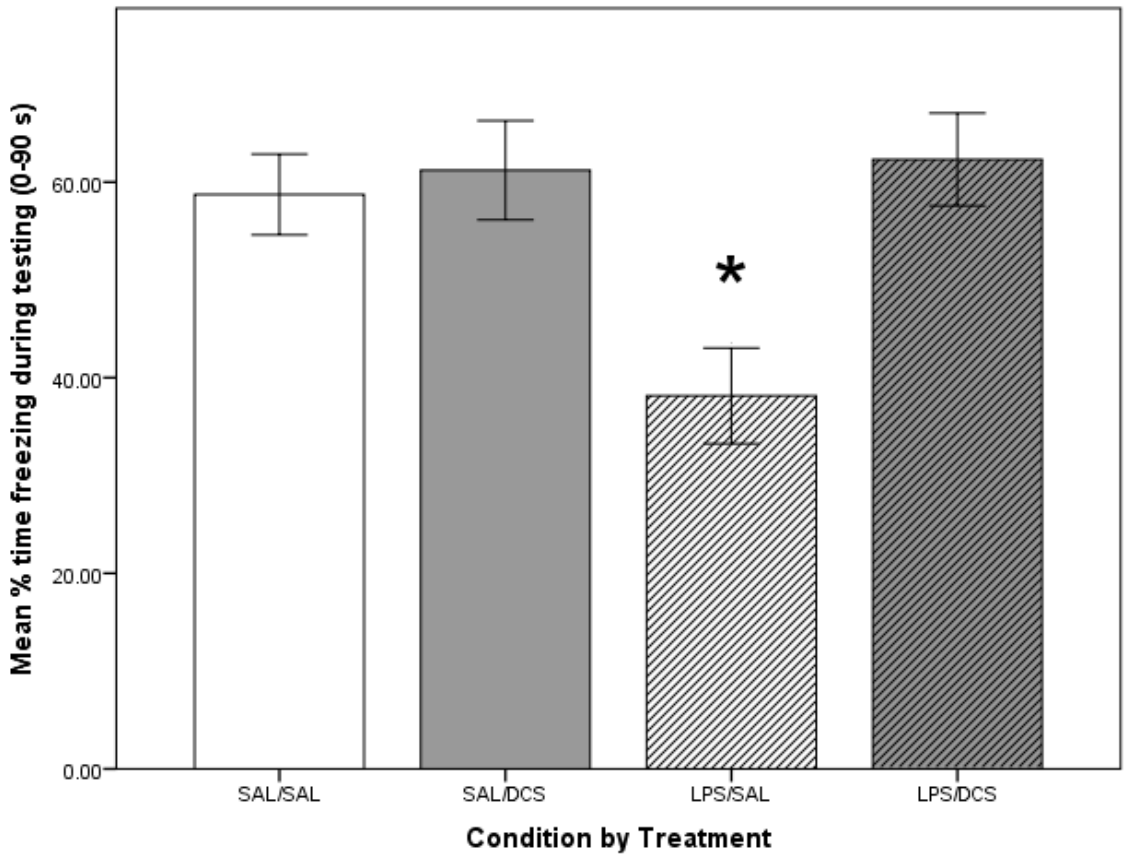

Figure 1: Post-training DCS administration rescues LPS-induced deficits in contextual fear memory consolidation. C57BL/6J mice administered LPS only (250 μg/kg, i.p.; LPS/SAL) froze less than mice that were administered saline only (SAL/SAL). Mice co-administered LPS and DCS (15 mg/kg, i.p.; LPS/DCS) froze the same amount as DCS only (SAL/DCS) treated mice. * Indicates a significant difference ($p < .05$) from the DCS treatment group within the LPS condition; $n = 9$ for all groups. Bars represent mean ± *SEM*.

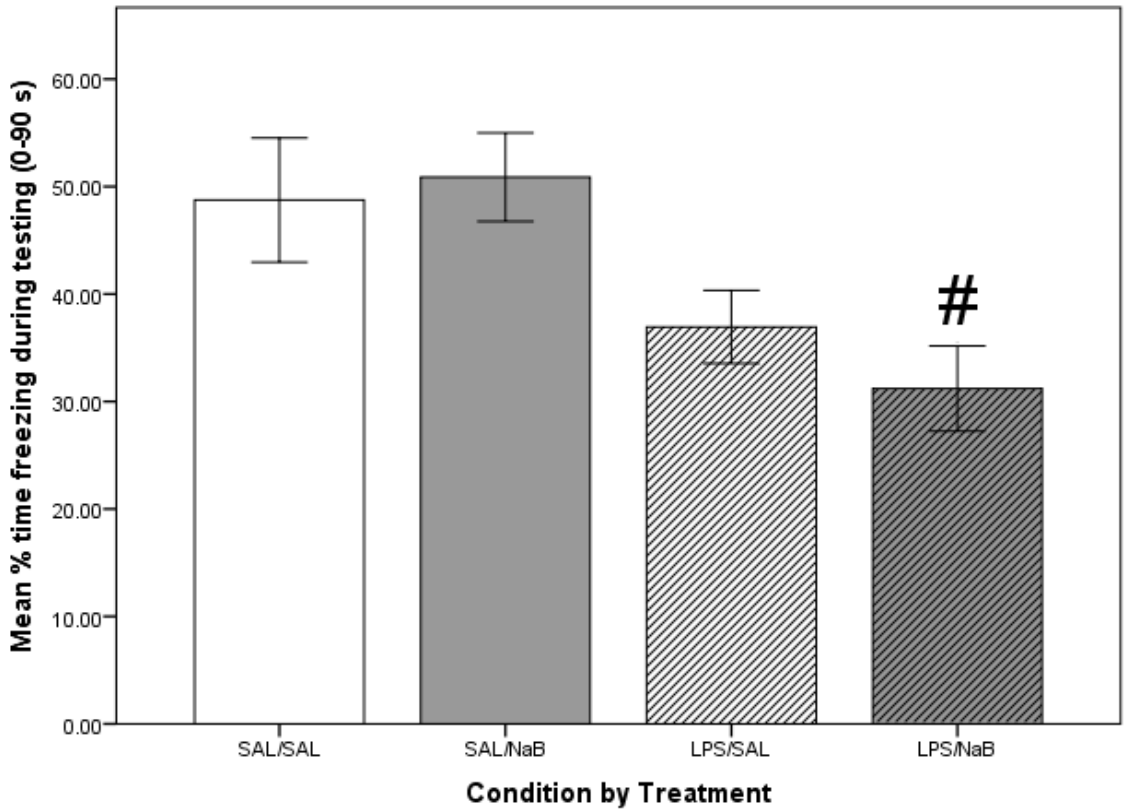

Figure 2: Post-training NaB administration does not rescue LPS-induced deficits in contextual fear memory consolidation. C57BL/6J mice administered LPS (250 μg/kg, i.p.) only (LPS/SAL) or co-administered LPS and NaB (1.2 g/kg; LPS/NaB) froze less than mice that were administered saline only (SAL/SAL) or NaB only (SAL/NaB). # Indicates a significant difference ($p < .05$) from the saline condition group within the NaB treatment; $n = 7$ for SAL/SAL; $n = 8$ for all other groups. Bars represent mean ± *SEM*.

Table 1: Descriptive statistics for Experiment 1

	DCS	Saline	**Condition total**
LPS	*M* = 62.32, *SEM* = 4.72	*M* = 38.15, *SEM* = 4.72	***M* = 50.23, *SEM* = 3.33**
Saline	*M* = 61.20, *SEM* = 4.72	*M* = 58.73, *SEM* = 4.72	***M* = 59.97, *SEM* = 3.33**
Treatment total	***M* = 61.76, *SEM* = 3.33**	***M* = 48.44, *SEM* = 3.33**	

Table 2: Descriptive statistics for Experiment 2

	NaB	Saline	**Condition total**
LPS	*M* = 31.20, *SEM* = 4.25	*M* = 36.94, *SEM* = 4.25	***M* = 34.07, *SEM* = 3.00**
Saline	*M* = 50.87, *SEM* = 4.25	*M* = 48.75, *SEM* = 4.54	***M* = 49.81, *SEM* = 3.11**
Treatment total	***M* = 41.04, *SEM* = 3.00**	***M* = 42.85, *SEM* = 3.11**	

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ABSTRACT

In mice, peripheral administration of the bacterial endotoxin lipopolysaccharide (LPS) activates the innate immune system, leading to deficits in hippocampus-dependent memory. D-cycloserine (DCS), a partial NMDA receptor agonist, has been shown to enhance memory consolidation in various hippocampus-dependent paradigms. Sodium butyrate (NaB), a histone deacetylase inhibitor, has been shown to have a strong anti-inflammatory effect *in vitro*, and to restore age-related deficits in memory consolidation in a hippocampus-dependent paradigm. In our first experiment, peripherally administered DCS restored appropriate memory consolidation following systemic LPS exposure, but DCS alone did not enhance memory consolidation. In our second experiment, peripherally administered NaB failed to restore appropriate memory consolidation following systemic LPS exposure, and NaB alone did not enhance memory consolidation. In summary, post-training administration of DCS, but not NaB, rescued LPS-induced deficits in memory consolidation.